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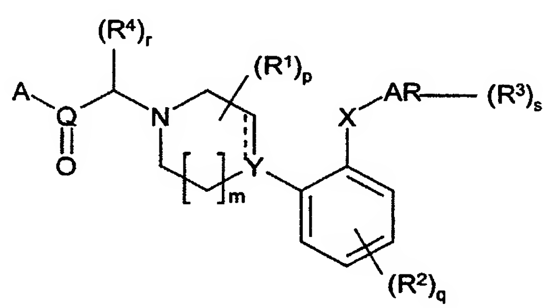
(54) Title: ARYLOXYPHENYL AND ARYLSULFANYLPHENYL DERIVATIVES



(I)

(57) Abstract: The invention provides compounds of the formula (I) wherein the substituents are as defined in the application. The compounds are valuable glycine transport inhibitors.

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Aryloxyphenyl and Arylsulfanylphenyl derivatives

The present invention relates to novel compounds which are glycine transporter inhibitors and as such effective in the treatment of disorders in the CNS.

Background of the invention

Glutamic acid is the major excitatory amino acid in the mammalian central nervous system (CNS), and acts through two classes of receptors, the ionotropic and metabotrobic receptors, respectively. The ionotropic glutamate receptors are divided into three subtypes based on the affinities of agonists for these receptors, namely *N*-methyl-D-aspartate (NMDA), (*R*,*S*)-2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA) and kainic acid (or kainate) receptors.

The NMDA receptor contains binding sites for modulatory compounds such as glycine and polyamines. Binding of glycine to its receptor enhances the NMDA receptor activation. Such NMDA receptor activation may be a potential target for the treatment of schizophrenia and other diseases linked to NMDA receptor dysfunction. An activation can be achieved by an inhibitor of the glycine transporter.

Molecular cloning has revealed the existence of two types of glycine transporters, GlyT-1 and GlyT-2, wherein GlyT-1 can be further subdivided into GlyT-1a, GlyT-1b and GlyT-1c.

The NMDA receptor is blocked by compounds such as phencyclidine which induce a psychotic state which resembles schizophrenia. Likewise, the NMDA antagonists, such as ketamine, induce negative and cognitive symptoms similar to schizophrenia. This indicates that NMDA receptor dysfunction is involved in the pathophysiology of schizophrenia.

The NMDA receptor has been associated with a number of diseases, such as pain (Yaksh *Pain* **1989**, 37, 111-123), spasticity, myuoclonus and epilepsy (Truong et. al.

Movement Disorders **1988**, 3, 77-87), learning and memory (Rison et. al. *Neurosci. Biobehav. Rev.* **1995**, 19, 533-552).

Glycine transporter antagonists or inhibitors are believed to be highly beneficial in the treatment of schizophrenia (Javitt WO 97/20533).

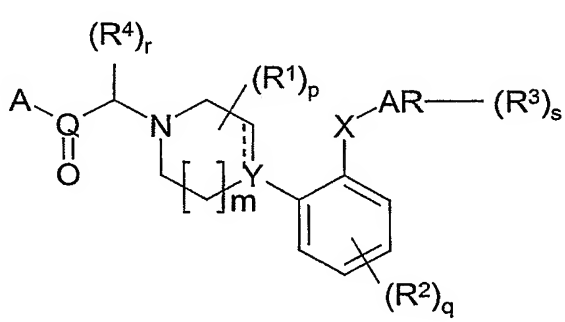
Glycine transport antagonists or inhibitors could be useful for the treatment of both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke. Likewise, convulsive disorders such as epilepsy, spasticity or myoclonus may benefit from glycine transporter antagonists.

Clinical trials with glycine have been reported, Javitt et. al. *Am. J. Psychiatry* **1994,** 151, 1234-1236 and Leiderman et. al. *Biol. Psychiatry* **1996**, 39, 213-215. The treatment with high-dose glycine is reported to improve the symptoms of schizophrenia. There is a need for more efficient compounds for the treatment of NMDA associated diseases.

The present invention provides compounds which are potent inhibitors of the glycine transporter and consequently they are useful in treating diseases associated with NMDA dysfunction.

Summary of the invention

The present invention provides compounds of the general formula I



I

Y is N, C or CH;

X represent O or S;

m is 1 or 2;

p is 0,1, 2, 3 or 4;

q is 0, 1 or 2;

s is 0, 1, 2 or 3;

r is 0, 1 or 2;

Q represents C, P-OR^5, or S=O, wherein R^5 represents hydrogen or C_{1-6}-alkyl;

A is OR^6 wherein R^6 represent hydrogen, C_{1-6}-alkyl, aryl or aryl-C_{1-6}-alkyl, wherein aryl may be substituted with halogen, CF_3, OCF_3, CN, NO_2 or C_{1-6} alkyl;

AR represents phenyl or a heterаryl;

Each R^4 individually represents C_{1-6}-alkyl, C_{3-8}-cycloalkyl or C_{3-8}-cycloalkyl-C_{1-6}-alkyl;

The dotted line represents an optional bond;

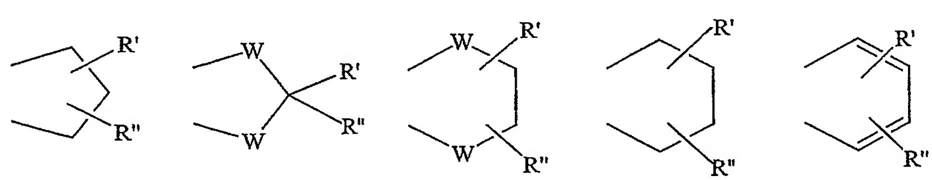
Each R^1, which may be identical or different, is independently selected from the group consisting of C_{1-6}-alkyl, or two R^1,s attached to the same carbon atom may form a 3-6-membered spiro-attached cyclo-alkyl;

Each R^2, which may be identical or different, is independently selected from the groups consisting of halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl, C_{1-6}-alk(en/yn)ylsulfonyl or $-NR^9R^{10}$ wherein R^9 and R^{10} independently represent hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl, or R^9 and R^{10} together form a 3-7-membered ring which optionally contains one further heteroatom;

Each R^3, which is substituted on AR, may be identical or different, is independently selected from a group consisting of halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)ylsulfonyl, aryl, aryl-C_{1-6}-alk(en/yn)yloxy, aryl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxycarbonyl, acyl, -NHCO-C_{1-6}-alk(en/yn)yl, -$CONR^{11}R^{12}$ wherein R^{11} and R^{12} independently represent hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl or aryl, or R^{11} and R^{12} together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

or $NR^{13}R^{14}$ wherein R^{13} and R^{14} independently represent hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl or aryl; or R^{13} and R^{14} together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

or two adjacent R^3 substituents together form a ring fused to the AR ring selected from the group consisting of



wherein W is O or S, and R' and R'' are hydrogen or C_{1-6}-alkyl:

or two adjacent R^3 substituents together form a heteroaryl containing one or two heteroatom fused to the AR,

or an acid addition salt thereof.

In case of the integers p, q, r or s being 0, the substituents are hydrogen.

If Y represents C, the dotted line is present. The dotted line is not present if Y represents N or CH.

The invention provides a compound of formula I as above for use as a medicament.

The invention provides a pharmaceutical composition comprising a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

The invention provides the use of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of diseases selected from the group consisting of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus.

The invention provides a method for the treatment of diseases selected from the group consisting of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound of formula I as above or a pharmaceutically acceptable acid addition salt thereof.

Detailed description of the invention

A preferred embodiment of the invention is wherein Y is N;
A preferred embodiment of the invention is wherein X is S;
A preferred embodiment of the invention is wherein Q is C;
A preferred embodiment of the invention is wherein A is OH;
A preferred embodiment of the invention is wherein p is 1 or 2.

A preferred embodiment of the invention is wherein m is 1;

A preferred embodiment of the invention is wherein q is 0.

A preferred embodiment of the invention is wherein r is 0 or 1;

A preferred embodiment of the invention is wherein s is 1 or 2.

A preferred embodiment of the invention is wherein AR is phenyl, thiophene, pyridyl, pyrimidyl, thiazolyl, imidazolyl or benzothizolyl;

A preferred embodiment of the above is wherein R^4 is CH_3;

A preferred embodiment of the invention is wherein AR is phenyl, r and q are both 0, p is 1 or 2, s is 1 or 2, r is 0 or 1; m is 1, R^1 is CH_3, A is OH, Q is C, Y is N and X is S;

An even more preferred embodiment of above is wherein each R^3 is independently selected from halogen, C_{1-6}-alkoxy or C_{1-6}-alkyl;

An even more preferred embodiment of the above is wherein R^3 is selected from the group consisting of Cl, F, OCH_3, t-butyl, 2-propyl or methyl;.

Particularly preferred embodiments of the invention are wherein the compound of the invention is any of the following:

(+/-)-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Fluoro-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*iso*-Propyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

(+/-)-2-{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-*trans*-2,5- dimethylpiperazin-1-yl}-propionic acid

{4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid

{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-2(R),5(S)-dimethyl-piperazin-1-yl}-acetic acid

{4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2,2-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[5-Chloro-2-(4-trifluoromethyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

{4-[5-Chloro-2-(3-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Phenyl-phenyloxy)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Methyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*iso*-Propyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-2-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-3-methylpiperazin-1-yl}-propionic acid

{4-[2-(4-Isopropyl-phenylsulfanyl)-phenyl]-piperazin-1-yl}-acetic acid

(+/-)-2-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-3-methyl-piperazin-1-yl}-propionic acid

or a pharmaceutically acceptable acid addition salt thereof.

Definition of substituents

Halogen means fluoro, chloro, bromo or iodo.

The expression C_{1-6}-alk(en/yn)yl means a C_{1-6}-alkyl, C_{2-6}-alkenyl, or a C_{2-6}-alkynyl group. The expression C_{3-8}-cycloalk(en)yl means a C_{3-8}-cycloalkyl- or cycloalkenyl group.

The term C_{1-6} alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6} alkenyl and C_{2-6} alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The term C_{3-8} cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C_{3-8} cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

In the term C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{1-6}-alk(en/yn)yl are as defined above.

The terms C_{1-6}-alk(en/yn)yloxy, C_{1-6} alk(en/yn)ylsulfanyl, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfonyl etc. designate such groups in which the C_{1-6}-alk(en/yn)yl are as defined above.

As used herein, the term C_{1-6}-alk(en/yn)yloxycarbonyl refers to groups of the formula C_{1-6}-alk(en/yn)yl-O–CO-, wherein C_{1-6}-alk(en/yn)yl are as defined above.

As used herein, the term acyl refers to formyl, C_{1-6}-alk(en/yn)ylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)ylcarbonyl or a C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-carbonyl group.

The term 3-7-membered ring optionally containing one further heteroatom as used herein refers to ring systems such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolyl, or 1-pyrazolyl, all of which may be further substituted with C_{1-6}-alkyl.

The term heteroaryl may represent 5-membered monocyclic rings such as 3*H*-1,2,3-oxathiazole, 1,3,2-oxathiazole, 1,3,2-dioxazole, 3*H*-1,2,3-dithiazole, 1,3,2-dithiazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1*H*-1,2,3-triazole, isoxazole, oxazole, isothiazole, thiazole, 1*H*-imidazole, 1*H*-pyrazole, 1*H*-pyrrole, furan or thiophene and 6-membered monocyclic rings such as 1,2,3-oxathiazine, 1,2,4-oxathiazine, 1,2,5-oxathiazine, 1,4,2-oxathiazine, 1,4,3-oxathiazine, 1,2,3-dioxazine, 1,2,4-dioxazine, 4*H*-1,3,2-dioxazine, 1,4,2-dioxazine, 2*H*-1,5,2-dioxazine, 1,2,3-dithiazine, 1,2,4-dithiazine, 4*H*-1,3,2-dithiazine, 1,4,2-dithiazine, 2*H*-1,5,2-dithiazine, 2*H*-1,2,3-oxadiazine, 2*H*-1,2,4-oxadiazine, 2*H*-1,2,5-oxadiazine, 2*H*-1,2,6-oxadiazine, 2*H*-1,3,4-oxadiazine, 2*H*-1,2,3-thiadiazine, 2*H*-1,2,4-thiadiazine, 2*H*-1,2,5-thiadiazine, 2*H*-1,2,6-thiadiazine, 2*H*-1,3,4-thiadiazine, 1,2,3-triazine, 1,2,4-triazine, 2*H*-1,2-oxazine, 2*H*-1,3-oxazine, 2*H*-1,4-oxazine, 2*H*-1,2-thiazine, 2*H*-1,3-thiazine, 2*H*-1,4-thiazine, pyrazine, pyridazine, pyrimidine, 4*H*-1,3-oxathiin, 1,4-oxathiin, 4*H*-1,3-dioxin, 1,4-dioxin, 4*H*-1,3-dithiin, 1,4-dithiin, pyridine, 2*H*-pyran or 2*H*-thiin.

The term aryl refers to carbocyclic, aromatic systems such as phenyl and naphtyl.

The acid addition salts of the invention are preferably pharmaceutically acceptable salts of the compounds of the invention formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (i.e. enantiomers or diastereomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

Pharmaceutical compositions

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the

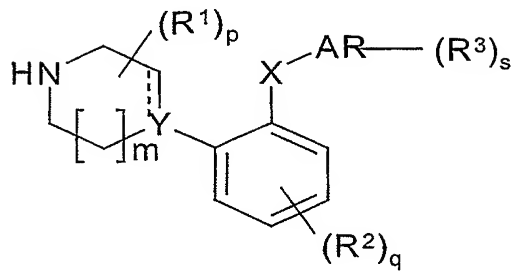
mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilising the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added. such as tonicity agents, preservatives, antioxidants, etc.

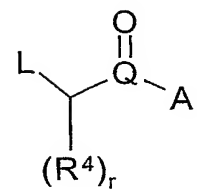
The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 100 mg. The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.

The compounds of the invention are prepared by the following general methods:
Alkylation of an amine of formula II with an alkylating agent of formula III



(II)

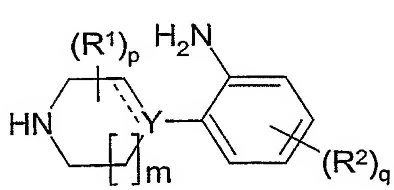


(III)

L is a suitable leaving group such as halogen or tosylate. The substituents AR, R^1-R^4,Y,Q, X, A, m, p,q, r and s are as defined above. The reaction is typically performed in a suitable solvent such as ethanol, N,N- dimethylformamide or acetonitrile containing an inorganic base such as potassium or cesium carbonate or an organic base such N-ethyl diisopropylamine at an elevated temperature of 40-120 °C. Compounds of formula I wherein Q is carbon and A is OR^6 wherein R^6 is hydrogen may be prepared from the corresponding esters $COOR^6$ wherein R^6 is an insoluble polymer or C_{1-6}-alkyl, aryl or aryl-C_{1-6}-alkyl. The transformation may be performed under basic conditions, for example, using aqueous sodium hydroxide in an alcoholic solvent or acidic conditions for R^6 being a tertiary-butyl group or an insoluble polymer.

Compounds of formula II may be prepared by any of the following reactions:.

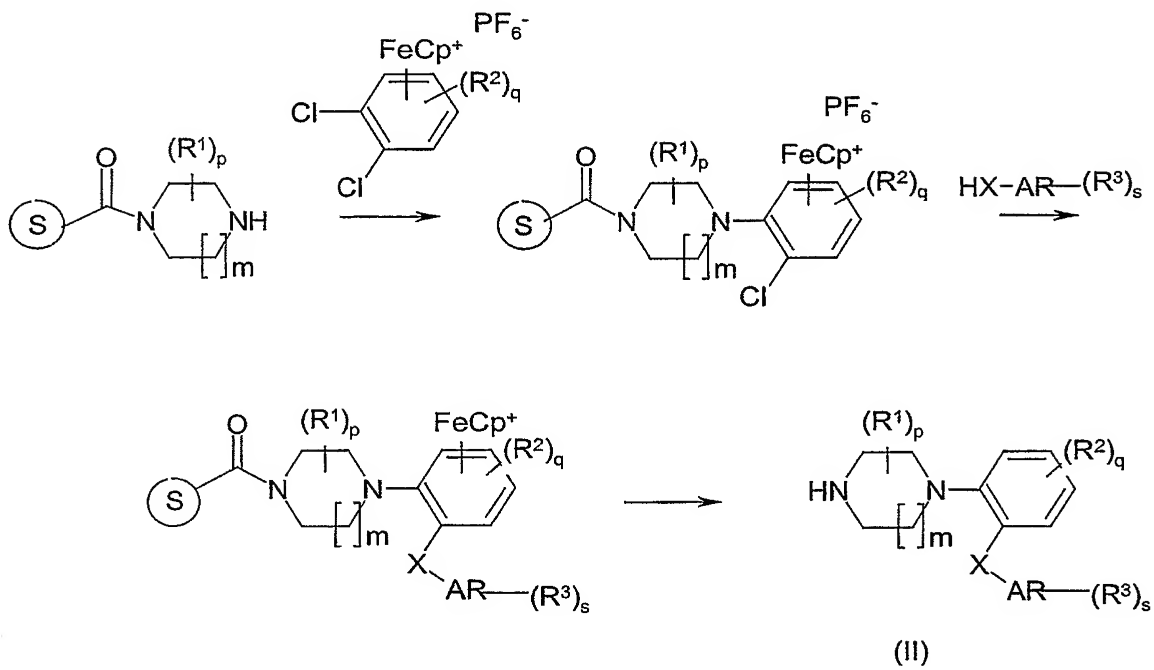
a) Chemical transformation of a compound with formula IV



IV

wherein R^1, R^2, m, p, q, X,Yand Z are as described above, to the corresponding diazonium compound, and subsequently react with a compound HX-AR-$(R^3)_s$, wherein AR, X, R^3 and s are as defined above.

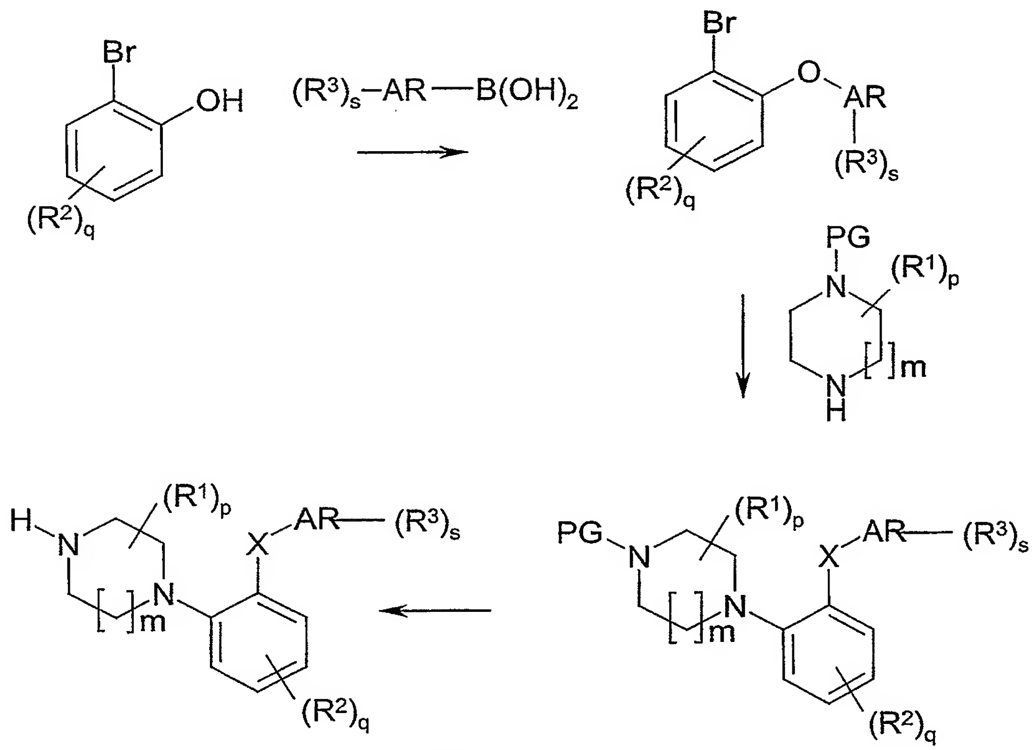
b) A chemical synthesis as depicted in scheme I



Scheme I

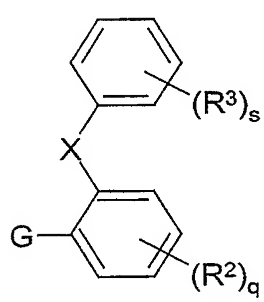
wherein AR, R^1, R^2, R^3, s, m, p, q and X are as described above and the circled S represents the solid support.

c) A chemical synthesis as depicted in scheme II where X is O and Y is N.



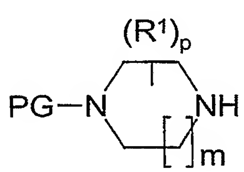
Scheme II

d) A chemical transformation of a compound of formula V



V

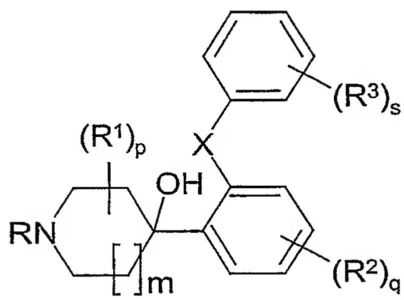
wherein R^2, R^3, X, s and q are as described above and G is a bromine or iodine atom with a compound of formula VI



VI

wherein R^1, m and p are as defined above.

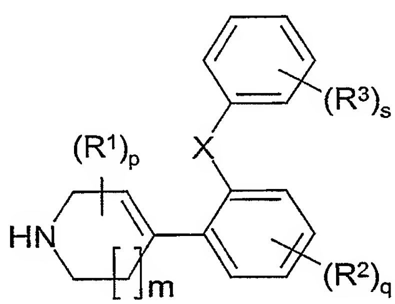
e) Dehydrating and optionally simultaneously deprotecting a compound of formula VII



VII

wherein R^1, R^2, R^3, X, m, p, q and s are as described above and R is either a hydrogen atom or a BOC group.

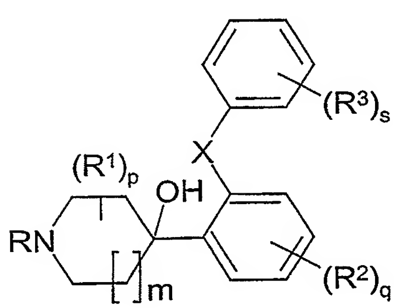
f) Hydrogenation of the double bond in a compound of formula VIII



VIII

wherein R^1, R^2, R^3, X, m, p, q and s are as described above.

g) Deoxygenation and deprotection of a compound of formula VII



VII

wherein R^1, R^2, R^3, X, m, p, q and s are as described above and R is either a hydrogen atom or a BOC group.

The diazotation followed by reaction with a compound HS-Ar-$(R^3)_s$ according to method a) is performed by addition of the diazonium salt of the corresponding aniline to a solution of sodium salt of a thiophenol in water containing a copper suspension. The starting material of formula IV is prepared as outlined in the following. A fluoronitrobenzene derivative is reacted with a piperazine derivative in a solvent such as DMF, NMP or other dipolar aprotic solvent containing an organic base such as triethylamine to afford the orthonitophenylpiperazine derivative. The nitro group is then reduced using standard procedures known to those skilled in the art to give the starting material of formula IV.

For 2,5-dimethylpiperazine derivatives the N-Benzyl-2(R),5(S)-dimethylpiperazine was prepared according to known literature procedures (Aicher et al *J. Med. Chem.* **2000**, *43*, 236-249). N-Benzyl-2(S),5(R)-dimethylpiperazine was prepared according to patent application WO 00/71535.

The reaction sequence in method b) is prepared according to the methods described in patent application WO 01/49681. The diamines are either commercially available or synthesised by methods known to chemists skilled in the art. Iron-complexes, like η^6-1,2-dichlorobenzene-η^5-cyclopentadienyliron(II) hexafluorophosphate and substituted analogues are synthesised according to literature known procedures (Pearson et al. *J. Org. Chem.* **1996,** *61*, 1297-1305) or synthesised by methods known to chemists skilled in the art.

The starting material in method c) is prepared by the coupling of an ortho bromophenol with a suitable aryl boronic acid or boronate ester in a known literature procedure (Evans et al, *Tet. Lett*, **1998**, 39, 2947-2940). The resulting biarylether bromide is then coupled using palladium catalysis to a protected piperazine where the protective group may be typically but not exclusively a tert-butyloxycarbonyl (BOC) derivative or benzyloxycarbonyl (CBZ) and the protecting group (PG) is then removed by acidic cleavage for example using hydrogen chloride in an alcoholic solvent for removal of the BOC group or catalytic hydrogenolysis in the case of the a

CBZ removed to give intermediates of formula II where X is O and Y is N. The general methods for removal of suitable protecting groups are described in the textbook *Protective Groups in Organic Synthesis* T.W.Greene and P.G.M. Wuts, Wiley Interscience, (1991) ISBN 0471623016.

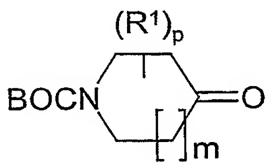
The reaction of a compound of formula V with a diamine of formula VI in method d) was performed in a similar manner as described in Nishiyama et al. *Tetrahedron Lett.* **1998,** *39*, 617-620. The starting material of formula VI was prepared in a similar manner as described in Schopfer et al. *Tetrahedron* **2001,** *57,* 3069-3073.

The dehydration reaction and optional simultaneous deprotection of a compound of formula VII in method e) was performed in a similar manner as described in Palmer et al *J. Med. Chem.* **1997**, *40*, 1982-1989. The starting material of formula VII was prepared from a compound of formula VII wherein R is a BOC group by deprotection with hydrochloric acid in methanol. Compounds of formula VII may be prepared as described in Palmer et al. *J. Med. Chem.* **1997**, *40*, 1982-1989.

The reduction of the double bond according to method f) is generally performed by catalytic hydrogenation at low pressure (< 3 atm.) in a Parr apparatus, or by using reducing agents such as diborane or hydroboric derivatives as produced *in situ* from $NaBH_4$ in trifluoroacetic acid in inert solvents such as tetrahydrofuran (THF), dioxane, or diethyl ether.

The deoxygenation of tertiary alcohol intermediates of formula VII in method g) wherein R is a BOC group, was performed by a modified Barton reduction in a similar manner as described in Hansen et al. *Synthesis* **1999**, 1925-1930. The intermediate tertiary alcohols were prepared from the corresponding properly substituted 1-bromo-phenylsulfanylbenzenes or their corresponding ethers by metal-halogen exchange followed by addition of an appropriate electrophile of the formula IX in a similar manner as described in Palmer et al. *J. Med. Chem.* **1997**, *40*, 1982-1989. The properly substituted 1-bromo-phenylsulfanylbenzenes were prepared in a similar manner as described in the literature by reaction of properly substituted thiophenols with properly substituted aryliodides according to Schopfer and

Schlapbach *Tetrahedron* **2001**, *57* 3069-3073 Bates et al., *Org. Lett.* **2002**, *4*, 2803-2806 and Kwong et al. *Org. Lett.* 2002, *4*, (in press). The corresponding substituted 1-bromo-phenoxybenzenes may be prepared as described by Buck et al. *Org. Lett.* **2002**, *4*, 1623-1626. Removal of the BOC group was performed by standard methods known to those skilled in the art



IX

Examples

General Methods

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmmetry C18 column with 3.5 μm particle size; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes.
Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 μm particle size; Method: Linear gradient elution with 80% A to 100% B in 7 min and with a flow rate of 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated methylenchloride (99.8%D), chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui =

quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

For ion-exchange chromatography, the following material was used: SCX-columns (1 g) from Varian Mega Bond Elut®, Chrompack cat. No. 220776. Prior to use, the SCX-columns were pre-conditioned with 10% solution of acetic acid in methanol (3 mL). For de-complexation by irradiation, a ultaviolet light source (300 W) from Philipps was used. As starting polymer supports for solid phase synthesis, Wang-resin (1.03 mmol/g, Rapp-Polymere, Tuebingen, Germany) was used.

Preparation of intermediates of formula IV

2-(3-Methylpiperazin-1-yl)phenylamine

2-Fluoronitrobenzene (7.1 g, 50 mmol) was dissolved in DMF (100 mL) containing triethylamine (10 g, 100 mmol) and placed under a nitrogen atmosphere. To the reaction was added 2-methylpiperazine (5.0 g, 50 mmol). The reaction was heated to 80 °C for 16 hours. The reaction was allowed to cool to room temperature before the solvent was reduced to half volume *in vacuo*. Ethyl acetate (200 mL) and ice-water (250 mL) were added to the solution and the product was extracted with diethylether (2 X 200 mL). The aqueous phase was saturated with sodium chloride and extracted with ethyl acetate (2 X 200 mL). The organic phases were combined, washed with saturated brine, dried over magnesium sulfate, filtered and the filtrate was concentrated *in vacuo*. The product (10.5 g) was dissolved in ethanol (250 mL). Palladium on charcoal catalyst (10% w/w, 2.2 g) was added to the solution and the solution was hydrogenated in a Parr apparatus at 3 bar for 3 hours. The solution was filtered and evaporated to give the aniline product. Yield (8.0 g, 83%)

The following intermediates were prepared in an analogous fashion:

2-(3,5-Dimethylpiperazin-1-yl)phenylamine
2-(3,3-Dimethylpiperazin-1-yl)phenylamine
4-Methoxy-2-(3-methylpiperzin-1-yl)phenylamine

2-(2(S),5(R)-Dimethylpiperazin-1-yl)phenylamine

2(R),5(S)-Dimethyl-1-N-benzyl-piperazine (6.0 g, 29 mmol) was dissolved in dimethylformamide (100 mL), and triethylamine (6.4 mL, 44 mmol) and the mixture was placed under nitrogen. To the solution was added 2-fluoro-nitrobenzene (3.5 mL, 31 mmol). The reaction was heated at 100 °C for 72 hours .The solution was evaporated *in vacuo* and redissolved in ethyl acetate (100 mL). The solution was then washed with saturated sodium bicarbonate solution (100 mL) and saturated brine solution (100 mL). The separated organic phase was dried over magnesium sulfate, filtered and the filtrate was evaporated *in vacuo*. The crude product was then purified by flash chromatography, eluting with ethyl acetate/methanol/triethylamine 85:10:5. The product (8.2 g) was dissolved in ethanol (250 mL). Palladium on charcoal catalyst (10% w/w, 2.2 g) was added to the solution and the solution was hydrogenated in a Parr apparatus at 3 bar for 3 hours. The solution was filtered and evaporated to give the aniline product. Yield (5.2 g, 87%)

The following intermediate were prepared in an analogous fashion

2-(2(R),5(S))-Dimethylpiperazin-1-yl)phenylamine

4-Chloro-2-(3,3-dimethyl-piperazin-1-yl)-phenylamine

2,2-Dimethylpiperazine (9.55g, 84 mmol) was dissolved in dimethylformamide (140 mL). To the solution was added triethylamine (12.07 mL, 83.6 mmol) and the reaction was placed under a nitrogen atmosphere. The solution was heated to 80 °C and 4-Chloro-2-fluoro-nitrobenzene (13.5g, 76 mmol) was added as a solution in dimethylformamide (35 mL). The reaction was stirred at 40°C for 16 hours. The solvent was removed *in vacuo* and the residue dissolved in ethanol (250 mL). Ammonium chloride (28 g) and zinc powder (17 g) were added. The reaction was boiled under reflux at 80 °C for 1 hour and then allowed to stir at 40 °C for 72 hours. The reaction was then filtered and the filtrate evaporated *in vacuo*. The solid was then washed with ethyl acetate and then a small amount of methanol- Yield: 16.04 g , 88%

The following intermediates were prepared in an analogous fashion

4-Chloro-2-(3 -(R)-methyl-piperazin-1-yl)-phenylamine

4-Chloro-2-(3 -(S)-methyl-piperazin-1-yl)-phenylamine

Preparation of intermediates of formula II by method a

1-[2-(4-Chloro-phenylsulfanyl)phenyl]-3-methylpiperazine

2-(3-Methylpiperazin-1-yl)phenylamine (0.96 g, 5 mmol) was dissolved in water (30 mL) containing concentrated sulfuric acid (0.28 mL, 5.2 mmol), the solution was cooled to 0 °C and sodium nitrite (0.36 g, 5.2 mmol) was added. The reaction was stirred for 30 minutes before the pH of the reaction was adjusted to pH 7 with sodium acetate. The diazonium salt solution was then added dropwise to a solution of 4-chlorothiophenol in 2 M NaOH (4 mL) containing a copper suspension (0.3 g, 5 mmol). After addition, the mixture was heated to 60 °C for 30 minutes before being allowed to cool to room temperature and ethyl acetate (10 mL) was added. The mixture was filtered and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 X 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified by flash chromatography using silica gel, eluting with ethyl acetate /methanol/ammonia 96:3:1. The pure product was isolated as a colourless oil. Yield (0.18 g ,11%) ^{1}H NMR ($CDCl_3$, 500 MHz) 1.12 (d, 3H); 2.6-2.72 (br m, 2H); 3.0-3.15 (m, 5H); 6.9 (m, 2H); 7.08 (d, 1H); 7.15 (m, 1H); 7.25-7.35 (m, 4H); MS (MH^+) 319.1.

The following compounds were prepared in an analogous fashion:

1-[2-(4-Chloro-phenlsulfanyl)phenyl]-3,5-dimethylpiperazine

(+/-)-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazine

(+/-)-{4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazine

(+/-)-{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazine

(+/-)-{4-[2-(4-Fluoro-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazine

(+/-)-4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-2-methyl-piperazine

(+/-)-4-[2-(4-iso-Propyl-phenylsulfanyl)-phenyl]-2-methyl-piperazine

4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazine

4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-2(R),5(S)-dimethyl-piperazine

Preparation of intermediates II according to method b where A represents an insoluble polymer

Preparation of iron complexes

η^6-1,2-Dichlorobenzene-η^5-cyclopentadienyliron(II) hexafluorophosphate

Ferrocene (167 g), anhydrous aluminium trichloride (238 g) and powdered aluminium (24 g) were suspended in 1,2-dichlorobenzene (500 mL) and heated to 90°C in a nitrogen atmosphere for 5 h with intensive stirring. The mixture was cooled to room temperature and water (1000 mL) was added carefully in small portions while cooling on an ice bath. Diethylether (500 mL) were added, and the mixture was stirred at room temperature for 30 minutes. The mixture was extracted with diethylether (3 x 300 mL). The aqueous phase was filtered, and aqueous ammonium hexafluorophosphate (60 g in 50 mL water) was added in small portions under stirring. The product was allowed to precipitate at room temperature. After 3 hours the precipitate was filtered off, washed intensively with water and dried *in vacuo* (50 °C) to give 81 g (21%) of the title compound as a light yellow powder. ^{1}H NMR (D_6-DMSO): 5.29 (s, 5H); 6.48 (m, 2H); 7.07 (m, 2H).

Preparation of polystyrene-bound amines

4-[(Piperazin-1-yl)carbonyloxymethyl]phenoxymethyl polystyrene

4-[(4-Nitrophenoxy)carbonyloxymethyl]phenoxymethyl polystyrene (267 g, 235 mmol) was suspended in dry N,N-dimethylformamide (2 L). N-Methylmorpholine (238.0 g, 2.35 mol) and piperazine (102.0 g, 1.17 mol) were added and the mixture was stirred at room temperature for 16 h. The resin was filtered off and washed with N,N-dimethylformamide (2 X 1 L), tetrahydrofuran (2 X 1 L), water (1 X 500 mL), methanol (2 X 1 L), tetrahydrofuran (2 X 1 L) and methanol (1 X 1 L). Finally, the resin was washed with dichloromethane (3 X 500 mL) and dried *in vacuo* (25 °C, 36 h) to yield an almost colourless resin (240.0 g).

The following polystyrene bound diamines were prepared analogously:

4-[(2,5-Dimethyl-piperazin-1-yl)carbonyloxymethyl]phenoxymethyl polystyrene

4-[(3-Methyl-piperazin-1-yl)carbonyloxymethyl]phenoxymethyl polystyrene

Preparation of resin-bound η^6-aryl-η^5-cyclopentadienyliron(II) hexafluorophosphates

4-({4-[η^6-(2-Chlorophenyl)-η^5-cyclopentadienyliron(II)]piperazin-1-yl}carbonyloxymethyl)phenoxymethyl polystyrene hexafluorophosphate

4-[(Piperazin-1-yl)carbonyloxymethyl]phenoxymethyl polystyrene (115.1 g, 92 mmol) was suspended in dry tetrahydrofuran (1.6 L), and η^6-1,2-dichlorobenzene-η^5-cyclopentadienyliron(II) hexafluorophosphate (76.0 g, 184 mmol) was added followed by potassium carbonate (50.9 g, 368 mmol). The reaction mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the resin was filtered off and washed with tetrahydrofuran (2 X 500 mL), water (2 X 250 mL), tetrahydrofuran (2 X 500 mL), water (2 X 250 mL), methanol (2 X 250 mL), dichloromethane (2 X 250 mL) and methanol (2 X 250 mL). Finally, the resin was washed with dichloromethane (3 X 500 mL) and dried *in vacuo* (25 °C, 36 h) to yield a dark orange resin (142 g).

The following polystyrene bound iron-complexes were prepared analogously:

4-({4-[η^6-(2-Chlorophenyl)-η^5-cyclopentadienyliron(II)]-2,5-dimethylpiperazin-1-yl}carbonyloxymethyl)phenoxymethyl polystyrene hexafluorophosphate

4-({4-[η^6-(2-Chlorophenyl)-η^5-cyclopentadienyliron(II)]-3-methylpiperazin-1-yl}carbonyloxymethyl)phenoxymethyl polystyrene hexafluorophosphate

Preparation of ortho-(arylsulfanyl)phenyl piperazines

(+/-)-1-[2-(4-Methylphenylsulfanyl)phenyl]-trans-2,5-dimethylpiperazine:

To a solution of 4-methylthiophenol (1.4 g, 9.8 mmol) in a 1:1 mixture of tetrahydrofuran/dimethylformamide (5 mL), sodium hydride (7.4 mmol, 60% in mineral oil) was carefully added at room temperature (Caution: Generation of hydrogen). The mixture was stirred for an additional 30 min after the generation of hydrogen had ceased. Subsequently, 4-({4-[η^6-(2-chloro-phenyl)-η^5-cyclopentadienyliron(II)]-trans-2,5-dimethyl-piperazin-1-yl}carbonyloxymethyl)phenoxymethyl polystyrene hexafluorophosphate (3.5 g, 2.45 mmol) was added and the mixture was stirred at 55 °C for 6 h. After cooling to room temperature, the resin was filtered off and washed with tetrahydrofuran (2 X 50 mL),

tetrahydrofuran/water (1:1) (2 X 50 mL), N,N-dimethylformamide (2 X 50 mL), water (2 X 50 mL), methanol (3 X 50 mL), tetrahydrofuran (3 X 50 mL), and subsequently with methanol and tetrahydrofuran (each 50 mL, 5 cycles). Finally, the resin was washed with dichloromethane (3 X 50 mL) and dried *in vacuo* (25 °C, 12 h) to yield a dark orange resin. The thus obtained resin and a 0.5 M solution of 1,10-phenanthroline in 3:1 mixture of pyridine/water (20 mL) was placed in light-transparent reactor tube. The suspension was agitated by rotation under irradiation with visible light for 12 h. The resin was filtered and washed with methanol (2 X 25 mL), water (2 X 25 mL) and tetrahydrofuran (3 X 25 mL) until the washing solutions were colourless (approx. 5 cycles) and the irradiation procedure was repeated until decomplexation was complete (approx. 5 cycles). After the decomplexation was completed, the resin was washed with dichlormethane (3 X 25 mL) and dried *in vacuo* (25 °C, 12 h) to obtain a light brown resin. 3.7 g (24 mmol) of the thus obtained resin were suspended in a 1:1 mixture of trifluoroacetic acid and dichlormethane (2 mL) and stirred at room temperature for 2.5 h. The resin was filtered off and washed with dichloromethane (5 X 0.5 mL). After evaporation of the filtrate from volatile solvents *in vacuo*, an orange oil was obtained. The crude product was purified by preparative LC-MS and subsequently by ion-exchange chromatography.

LC/MS (m/z) 313.2 (MH^+); RT = 2.17; purity (UV, ELSD): 87.1%, 98.7%; yield: 47.8 mg (6%).

The following arylpiperazines were prepared analogously:

(+/-)-1-[2-(4-Isopropylphenylsulfanyl)phenyl]-trans-2,5-dimethylpiperazine
(+/-)-1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]-trans-2,5-dimethylpiperazine
(+/-)-1-[2-(4-Tertbuytylphenylsulfanyl)phenyl]-trans-2,5-dimethyl-piperazine
(+/-)-1-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-2-methyl-piperazine
(+/-)-1-[2-(4-Isopropyl-phenylsulfanyl)-phenyl]-piperazine

Preparation of intermediates of formula III where A is an insoluble polymer

4-[Chloroacetoxymethyl]phenoxymethyl polystyrene

Wang resin (10 g, 10.3 mmol) was suspended in dichloromethane (100 mL) and cooled to 0°C. Diisopropylethylamine (9 mL, 52 mmol) was added. Chloroacetylchloride was added slowly. The reaction mixture was stirred at 0 °C for 30 min and then allowed to heat to room temperature. The reaction mixture was stirred at room temperature for 16 h. The resin was filtered off and washed with N,N-dimethylformamide (3 X 100 mL), dichloromethane (2 X 100 mL), dimethylformamide (3 X 100 mL) and dichloromethane (2 X 100 mL) and dried *in vacuo* (25 °C, 16 h).

The following resin was prepared in an analogous fashion:
4-[2-Chloropropionyloxymethyl]phenoxymethyl polystyrene

Preparation of Intermediates II by method c

4-(2-Bromo-phenoxy)-biphenyl

A mixture of 2-bromophenol (2.08 g, 12 mmol), 4-biphenylboronic acid (4.75 g, 24 mmol), $Cu(OAc)_2$ (2.20 g, 12 mmol) and triethylamine (6.1 g, 60 mmol) in dioxane (100 mL) was stirred for 48 h. The crude mixture was evaporated onto silica gel and purified by column chromatography eluting with ethyl acetate/heptane 1:9.Yield: 0.73 g (19%). ^1H NMR ($CDCl_3$, 500 MHz) 7.65 (m, 1H) 7.55 (m, 4H), 7.43 (m, 2H), 7.25-7.38 (m, 2H), 7.00-7.08 (m, 4H); MS(m/z): 325.1.

(+/-)-1-[2-(Biphenyl-4-yloxy)-phenyl]-3-methyl-piperazine

A mixture of 4-(2-bromo-phenoxy)-biphenyl (0.73 g, 2.25 mmol), rac-2-methylpiperazine (0.285 g, 0.285 mmol), Pd_2dba_3 (0.022 g, 1 mol%), rac-binap (0.043 g, 3 mol%) and $NaOBu^t$ (0.300 g, 3.12 mmol) in dry toluene (15 mL) under argon and stirred at 90 °C overnight. After cooling to room temperature the mixture is filtered and evaporated onto silica gel and and purified by column chromatography eluting with ethyl acetate/heptane 1:2. Yield: 0.264 g (34%). ^1H NMR ($CDCl_3$, 500 MHz) 7.55 (m, 2H), 7.49 (m, 2H), 7.38 (m, 2H), 7.27 (m, 1H), 7.10 (m, 1H), 6.90-7.00 (m, 5H), 3.30-3.35 (m, 2H), 2.88 (m, 1H), 2.62-2.80 (m, 3H), 2.30-2.40 (m, 1H) 1.60-2.00 (br, 1H), 0.99 (d, 3H); MS(m/z): 345.1.

Preparation of compounds of the invention

Example 1

***1a** (+/-)-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride*

4-[2-(4-Methoxyphenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazine (0.5 g, 1.5 mmol) and N-ethyldisopropylamine (0.315mL, 1.8mmol) was dissolved in acetonitrile (10 mL) and placed under a nitrogen atmosphere. Ethyl bromoacetate (0.19 mL, 1.7 mmol) was added and the mixture was stirred at ambient temperature for 16 hours. To the mixture was then added a small amount of silica gel and the solvent was evaporated *in vacuo*. The product, absorbed on to silica gel, was poured on to a silica cartridge and eluted with dichloromethane/heptane/ethyl acetate (60:35:5). The ester was isolated from relevant fractions as a light oil (300 mg, 48%). The ester was then dissolved in ethanol (10 mL) and 2N NaOH was added (5 mL). The reaction was stirred for 16 hours at room temperature. The reaction was evaporated *in vacuo* and the residue was dissolved in ethyl acetate (50 mL). 2N HCl (15 mL) was added and the phases were separated. The aqueous phase was reextracted with ethyl acetate (2 X 50mL). The combined organic fractions were dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in a small amount of dichloromethane, precipitated by the addition of heptane and the solvent was removed *in vacuo*. Yield (280 mg, 100%). ^1H NMR ($CDCl_3$, 500 MHz) 0.87 (d, 3H), 1.35 (d, 3H), 3.04 (m,1H), 3.12 (m, 2H), 3.6 (m, 3H), 4.11 (d,1H), 4.31(d, 1H), 3.81 (s, 3H), 6.55 (d, 1H), 7.02 (d, 2H), 7.13 (dd, 1H), 7.2 (m, 1H), 7.42 (d, 2H) , LC-MS (m/z) $(MH)^+$ 387.4 RT=2.22 (UV, ELSD) 98%, 97%

and the following compounds were prepared in an analogous fashion:

***1b** (+/-)-{4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride*

^1H NMR ($CDCl_3$, 500MHz) 0.80 (d, 3H), 1.28 (d, 3H), 2.92-3.18 (m, 3H), 3.64 (m, 3H), 4.06 (d, 1H), 4.29 (d, 1H), 6.78 (d, 1H), 7.12 (t, 1H), 7.26 (m, 2H), 7.50 (m, 4H), LC-MS (m/z) (MH^+) 391.2 RT=2.43 (UV, ELSD) 99%, 99%. Yield 420 mg.

1c (+/-)-{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride

^{1}H NMR ($CDCl_3$, 500MHz) 0.76 (d, 3H), 1.01 (d, 3H), 1.30 (s, 9H), 2.4-2.6 (m, 2H), 2.9-3.0 (m, 3H), 3.28 (m, 1H), 3.32 (d, 1H), 3.48 (d, 1H), 6.65 (d, 1H), 7.01 (t, 1H), 7.13 (t, 1H), 7.24 (d, 1H), 7.39 (d, 2H), 7.47 (d, 2H), LC-MS (m/z) (MH^+) 412.9 RT=2.70 (UV, ELSD) 95%, 99%. Yield 550 mg.

1d (+/-)-{4-[2-(4-Fluoro-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride

^{1}H NMR ($CDCl_3$, 500MHz) 0.80 (d, 3H), 1.25 (d, 3H), 2.8-3.0 (m, 2H), 3.08 (m, 1H), 3.4-3.6 (m, 3H), 3.87 (d, 1H), 4.06 (d, 1H), 6.64 (d, 1H), 7.07 (m, 1H), 7.20 (m, 1H), 7.26 (m, 1H), 7.32 (dd, 2H), 7.54 (dd, 2H), LC-MS (m/z) (MH^+) RT=2.24 (UV, ELSD) 95%, 99%. Yield 180 mg.

1e (+/-)-{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid, hydrochloride

LC/MS (m/z) 399.2 (MH^+); RT = 2.54; purity (UV, ELSD): 100%, 100%; yield: 10.4 mg.

1f (+/-)-{4-[2-(4-iso-Propyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid, hydrochloride

LC/MS (m/z) 385.1 (MH^+); RT = 2.45; purity (UV, ELSD): 88%, 100%; yield: 11 mg.

1g (+/-)- 2-{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-trans 2,5 dimethylpiperazin-1-yl}-propionic acid, hydrochloride

LC/MS (m/z) 427.0 (MH^+); RT = 2.76; purity (UV, ELSD): 86%, 98%; yield: 27 mg.

1h {4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid, hydrochloride

^{1}H NMR (DMSO, 500 MHz) 1.40 (d, 3H), 3.16 (m,1H), 3.25-3.48 (m, 4H), 3.63 (m, 1H), 3.75 (m, 1H), 3.80 (s, 3H), 4.15 (d, 1H), 4.30 (d, 1H) 6.55 (d, 1H), 7.02 (d, 2H), 7.13 (dd, 1H), 7.2 (m, 1H), 7.42 (d, 2H)

LC/MS (m/z) 407.3 (MH^+); RT = 2.79; purity (UV, ELSD): 95%, 100%; yield: 225 mg.

1i {4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-2(R), 5(S)-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride

^{1}H NMR (DMSO–d6, 500 MHz) 0.85 (d, 3H), 1.30 (d, 3H), 2.95 (t,1H), 3.05 (m, 2H) 3.53 (d, 1H), 3.60-3.65 (m, 2H), 3.80 (m, 3H), 3.92 (d, 1H), 4.10 (d, 1H), 6.55 (d, 1H), 7.02 (d, 2H), 7.13 (dd, 1H), 7.2 (m, 1H), 7.42 (d, 2H)

LC/MS (m/z) 387.3 (MH^+); RT = 2.22; purity (UV, ELSD): 97%, 96.9%; yield: 607 mg.

1j {4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2,2-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride

^{1}H NMR (DMSO-d6, 500 MHz) 1.58 (s, 6H), 3.20 (s,2H), 3.20-3.60 (br m, 4H), 3.80 (s, 3H), 3.92 (d, 1H), 4.10 (d, 1H), 6.55 (d, 1H), 6.90 (dd, 1H), 6.96 (d, 2H), 7.13 (s, 1H), 7.40 (d, 2H)

LC/MS (m/z) 421.1 (MH^+); RT = 2.41; purity (UV, ELSD): 96%, 98%; yield: 1.18 g.

1k {4-[5-Chloro-2-(4-trifluoromethyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid, hydrochloride

LC/MS (m/z) 445.1 (MH^+); RT = 2.50; purity (UV, ELSD): 88%, 72%; yield: 20 mg.

1l {4-[5-Chloro-2-(3-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid, hydrochloride

^{1}H NMR (DMSO-d6, 500 MHz) 1.32 (d, 3H), 3.05 (m, 1H) 3.10-3.40 (m, 4H), 3.50-3.60 (m, 2H), 4.10 (d, 1H), 4.24 (d, 1H), 6.82 (d, 1H), 6.95 (m, 3H), 7.11 (dd, 1H), 7.2 (s, 1H), 7.38 (dd, 1H)

LC/MS (m/z) 407.2 (MH^+); RT = 2.41; purity (UV, ELSD): 99.6%, 100.%; yield: 1.26g

1m *{4-[2-(Biphenyl-4-yloxy)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid, hydrochloride*

^{1}H NMR (DMSO-d6, 500 MHz) 7.60 (m, 4H), 7.40 (m, 2H), 7.32 (m, 1H), 6.95-7.20 (m, 6H), 5.00-6.50 (br, 1H), 4.00-4.10 (m, 1H), 3.80-3.90 (m, 1H), 3.20-3.50 (m, 6H), 3.05-3.15 (m, 1H), 1.17 (m, 3H);
LC/MS (m/z) 403.0; RT= 2.45; purity: (UV/ELSD): 96.7% , 99.4; yield: 0.116 g (43 %)

Example 2

2a *(+/-)-{4-[2-(4-Methyl-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride*
A solution of [2-(4-Methyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazine (10 mg, 0.03 mmol) and diisopropylethylamine (0.02 mL, 0.11 mmol) was added to 4-[Chloroacetoxymethyl]phenoxymethyl polystyrene (100 mg, 0.09 mmol). The reaction mixture was agitated by shaking overnight at 70 °C. The resin was filtered off and washed with N,N-dimethylformamide (4 mL), methanol (4 mL) and dichloromethane (4 mL). The resin was suspended in a 1:1 mixture of trifluoroacetic acid and dichlormethane (1.5 mL) and shaken at room temperature for 1 h. The resin was filtered off and washed with dichloromethane (1 mL). The organic extracts were collected and evaporated in vacuo. The crude product was purified by preparative LC-MS.
LC/MS (m/z) 371.1 (MH^+); RT = 2.24; purity (UV, ELSD): 100%, 100%; yield: 1.6 mg.

The following compounds were prepared in an analogous fashion:

2b *(+/-)-{4-[2-(4-iso-Propyl-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride*
LC/MS (m/z) 399.0 (MH^+); RT = 2.48; purity (UV, ELSD): 98.3%, 100%; yield: 2.2 mg.

2c (+/-)-{4-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-trans-2,5-dimethyl-piperazin-1-yl}-acetic acid, hydrochloride

LC/MS (m/z) 385.0 (MH^+); RT = 2.37; purity (UV, ELSD): 99.8%, 100%; yield: 4.7 mg.

2d (+/-)-2-{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-3-methylpiperazin-1-yl}-propionic acid, hydrochloride

LC/MS (m/z) 386.7 (MH^+); RT = 2.14; purity (UV, ELSD): 91.9%, 99.2%; yield: 3.2 mg.

2e (+/-)-{4-[2-(4-Isopropyl-phenylsulfanyl)-phenyl]-piperazin-1-yl}-acetic acid, hydrochloride

LC/MS (m/z) 370.8 (MH^+); RT = 2.35; purity (UV, ELSD): 89.0.%, 99.9%; yield: 3.2 mg.

2f (+/-)-*2-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-3-methyl-piperazin-1-yl}-propionic acid, hydrochloride*

LC/MS (m/z) 386.7 (MH^+); RT = 2.63; purity (UV, ELSD): 91.9%, 99.2%; yield: 3.2 mg.

Pharmacological testing

The compounds of the invention were tested in a well-recognised and reliable test measuring glycine uptake:

[^{3}H]-Glycine uptake

Cells transfected with the human GlyT-1b were seeded in 96 well plates. Prior to the experiment the cells were washed twice in HBS (10 mM Hepes-tris (pH 7,4), 2,5 mM KCl, 1 mM $CaCl_2$, 2,5 mM $MgSO_4$,) and pre-incubated with test compound for 6 minutes. Afterwards, 10 nM ^{3}H-glycine was added to each well and the incubation

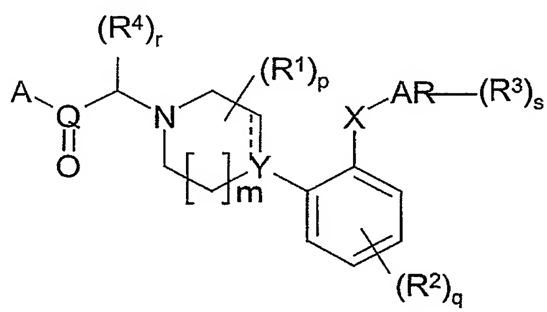
was continued for 15 minutes. The cells were washed twice in HBS. Scintillation fluid was added and the Plates were counted on a Trilux (Wallac) scintillation counter.

The test results showed, that the compounds of the invention all showed inhibition below 2000 nM as IC_{50} in the above-mentioned assay. Most of the compounds were between 150nM and 850nM.

Microdialysis experiments in rodents showed that administration of selected compounds of the invention resulted in an increased concentration of glycine in the brain. Furthermore, in a rodent model of psychosis, selected compounds of the invention reversed the symptoms of amphetamine induced hyperactivity.

Claims:

1. A compound represented by the general formula I



I

Y is N, C or CH;

X represent O or S;

m is 1 or 2;

p is 0,1, 2, 3 or 4;

q is 0, 1 or 2;

s is 0, 1, 2 or 3;

r is 0, 1 or 2;

Q represents C, P-OR^5, or S=O, wherein R^5 represents hydrogen or $C_{1\text{-}6}$-alkyl;

A is OR^6, wherein R^6 represent hydrogen, $C_{1\text{-}6}$-alkyl, aryl or aryl-$C_{1\text{-}6}$-alkyl, wherein aryl may be substituted with halogen, CF_3, OCF_3, CN, NO_2 or $C_{1\text{-}6}$ alkyl;

AR represents phenyl or a heterarAryl;

Each R^4 individually represents $C_{1\text{-}6}$-alkyl, $C_{3\text{-}8}$-cycloalkyl or $C_{3\text{-}8}$-cycloalkyl-$C_{1\text{-}6}$-alkyl;

The dotted line represents an optional bond;

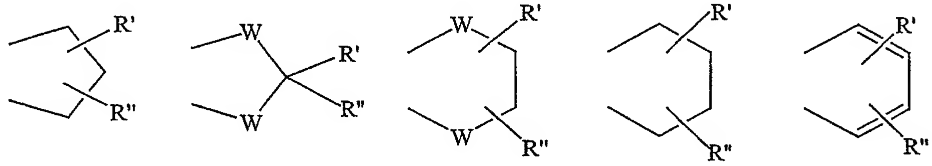
Each R^1 is independently selected from the group consisting of $C_{1\text{-}6}$-alkyl, or two R^1 attached to the same carbon atom may form a 3-6-membered spiro-attached cycloalkyl;

Each R^2 is independently selected from the groups consisting of halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(en/yn)yloxycarbonyl, C_{1-6}-alk(en/yn)ylsulfonyl or $-NR^9R^{10}$ wherein R^9 and R^{10} independently represent hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6} alk(en/yn)yl or aryl, or R^9 and R^{10} together form a 3-7-membered ring which optionally contains one further heteroatom;

Each R^3, which is substituted on AR, is independently selected from a group consisting of halogen, cyano, nitro, C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxy, C_{1-6}-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yloxy, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)ylsulfonyl, aryl, aryl-C_{1-6}-alk(en/yn)yloxy, aryl-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(en/yn)yloxycarbonyl, acyl, -NHCO-C_{1-6}-alk(en/yn)yl, -CONR^{11}R^{12} wherein R^{11} and R^{12} independently represent hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl or aryl, or R^{11} and R^{12} together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

or NR^{13}R^{14}wherein R^{13} and R^{14} independently represent hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl or aryl; or R^{13} and R^{14} together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

or two adjacent R^3 substituents together form a ring fused to the AR, selected from the group consisting of



wherein W is O or S, and R' and R'' are hydrogen or C_{1-6}-alkyl:

or two adjacent R^3 substituents together form a fused heteroaromatic system containing one or two heteroatoms fused to AR,

or an acid addition salt thereof.

2. The compound according to claim 1 wherein Y is N.

3. The compounds according to any of the above claims wherein X is S.

4. The compound according to any of the above claims wherein Q is C.

5. The compound according to any of the claims above wherein A is OH.

6. The compound according to any of the claims above wherein p is 1 or 2.

7. The compound according to any of the claims above wherein m is 1.

8. The compound according to any of the claims above wherein q is 0.

9. The compound according to any of the claims above wherein r is 0 or 1.

10. The compound according to any of the claims above wherein s is 1 or 2.

11. The compound according to any of the claims above wherein AR represents phenyl, thiophene, pyridyl, pyrimidyl, thiazolyl, imidazolyl or benzothizolyl.

12. The compound according to claims 1- 11 wherein AR is phenyl, r and q are both 0, p is 1 or 2, s is 1 or 2, r is 0 or 1; m is 1, R^1 is CH_3, A is OH, Q is C, Y is N and X is S.

13. The compound according to claim 12 wherein each R^3 is independently selected from halogen, C_{1-6}-alkoxy or C_{1-6}-alkyl.

14. The compound according to claim 13 wherein R^3 is selected from the group consisting of Cl, F, OCH_3, t-butyl, 2-propyl or methyl.

15. The compound according to any of the above wherein R^4 is CH_3.

16. The compound according to claim 1, said compound being

(+/-)-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Fluoro-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*iso*-Propyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

(+/-)-2-{4-[2-(4-tert-Butyl-phenylsulfanyl)-phenyl]-*trans*-2,5- dimethylpiperazin-1-yl}-propionic acid

{4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid

{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-2(R),5(S)-dimethyl-piperazin-1-yl}-acetic acid

{4-[5-Chloro-2-(4-methoxy-phenylsulfanyl)-phenyl]-2,2-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[5-Chloro-2-(4-trifluoromethyl-phenylsulfanyl)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

{4-[5-Chloro-2-(3-methoxy-phenylsulfanyl)-phenyl]-2(R)-methyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Phenyl-phenyloxy)-phenyl]-2-methyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-Methyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(4-*iso*-Propyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-{4-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-*trans*-2,5-dimethyl-piperazin-1-yl}-acetic acid

(+/-)-2-{4-[2-(4-*tert*-Butyl-phenylsulfanyl)-phenyl]-3-methylpiperazin-1-yl}-propionic acid

{4-[2-(4-Isopropyl-phenylsulfanyl)-phenyl]-piperazin-1-yl}-acetic acid

(+/-)-2-{4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-3-methyl-piperazin-1-yl}-propionic acid

or a pharmaceutically acceptable acid addition salt thereof.

17. A pharmaceutical composition comprising a compound according to claims 1 to 16 or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

18. The use of a compound according to claims 1 to 16 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of diseases selected from the group consisting of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus.

19 A method for the treatment of an illness selected from the group consisting of the positive and the negative symptoms of schizophrenia, including both the positive and the negative symptoms of schizophrenia and other psychoses, and in the improvement of cognition in conditions where the cognitive processes are diminished, i.e. Alzheimer's disease, multi-infarct dementia, AIDS dementia, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis or diseases wherein the brain is damaged by inner or outer influence, such as trauma to the head or stroke, and convulsive disorders such as epilepsy, spasticity or myoclonus

in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound according to claims 1 to 16 or a pharmaceutically acceptable acid addition salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 02/00859

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 241/04, C07D 295/15, A61K 31/495, A61P 25/18, A61P 25/28, A61P 25/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of Medicinal Chemistry, Volume 21, no. 12, 1978, Judith A. Kiritsy et al: "Synthesis and Quantitative Structure-Activity Relationships of Some Antibacterial 3-Formylrifamycin SV N-(4-Substituted phenyl)piperazinoacethydrazones", page 1301 - page 1307, page 1303, compound 3g --	1-2,4,7-9,11
X	WO 9817651 A1 (NEUROSEARCH A/S), 30 April 1998 (30.04.98), claims 1, 12, the examples --	1-19

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 April 2003	15 -04- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1998:366903, Document no. 129:95508, Yoshitomi Pharmaceutical Industries, Ltd.: "Preparation and formulation of piperazine derivatives as antipsychotics"; & JP,A2,10152470, 19980609	1-19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

29/03/03

International application No.

PCT/DK 02/00859

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9817651 A1	30/04/98	AU 726447 B	09/11/00
		AU 4616197 A	15/05/98
		CN 1234025 A	03/11/99
		CZ 9901272 A	15/09/99
		EP 0934281 A	11/08/99
		JP 2001502675 T	27/02/01
		NZ 334868 A	23/02/01
		SK 42499 A	16/05/00
		US 6218547 B	17/04/01
		US 6503925 B	07/01/03

Form PCT/ISA/210 (patent family annex) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00859

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 19 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.